The Relative Merits of Haemoglobin A_{1c} and Fasting Plasma Glucose as First-line Diagnostic Tests for Diabetes Mellitus in Non-pregnant Subjects

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HbA_{1c} was measured by high-performance ion-exchange chromatography in 401 non-pregnant patients undergoing oral glucose tolerance tests (OGTT). All those with HbA_{1c}>6.2 % (reference range 3.8–5.5 %) had diabetic OGTT (sensitivity 41 %, specificity 100 %). Although a fasting plasma glucose (FPG) cut-off $\geq$7.0 mmol l^{-1}, as recommended by the American Diabetes Association (ADA), had greater sensitivity (78 %), false positives (12 %) limited its usefulness, so more diagnostic confidence could be placed in a positive HbA_{1c}. In agreement with the ADA, we found FPG gave only slightly lower diabetes prevalence than the OGTT, but this masked a significant number of individual discrepancies (false positives and negatives) cancelling out each other. The new ADA category of impaired fasting glucose did not correlate well with impaired glucose tolerance. HbA_{1c} is insufficiently sensitive as a direct substitute for the OGTT. A third of subjects diabetic on OGTT had normal HbA_{1c} values, so it cannot exclude diabetes as currently defined, but HbA_{1c} screening could make sufficient positive diagnoses to reduce our non-pregnant OGTTs by one-fifth. If a 'risk threshold' for diabetic complications could be applied to HbA_{1c}, it could replace the OGTT as a more pragmatic diagnostic/prognostic test. © 1998 John Wiley & Sons, Ltd.

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Introduction

Much work has been done and many papers written in attempts to find suitable alternatives to the rather complicated and time-consuming oral glucose tolerance test (OGTT) for identifying people with diabetes. The presence of glycosuria, the fasting plasma glucose concentration (FPG) and the haemoglobin A_{1c} (HbA_{1c}) have all been found to be less sensitive than the plasma glucose concentration at 2 h after a 75 g glucose load. Often this work has been carried out in the context of population screening for epidemiological studies, but some workers have sought to employ these simpler tests as screening procedures to limit the number of OGTTs needed for diagnostic testing of individuals suspected of having diabetes. FPG works quite well for this purpose and has been found to be capable of a sensitivity approaching 60 % with a specificity of around 97 %.[1–3] Recently, the American Diabetes Association (ADA) has gone a stage further and recommended its use instead of the OGTT for routine clinical diagnostic purposes.[4] FPG, like the OGTT, suffers from the need for fasting and the uncertainty of patient compliance. HbA_{1c} on the other hand, requires no fasting, but is beset by difficulties of standardization and variability in results produced by different methods in different laboratories, leading to different reference ranges.

Initially, we attempted to ascertain whether the use of very similar HbA_{1c} methods in two different cities in the UK could provide valid and similar diagnostic information that was in keeping with the results of the standard OGTT. Our preliminary study indicated that the populations of patients in the two centres had similar prevalence of diabetes and our methods produced comparable diagnostic results.[5] The study was therefore extended and the results from the two sites pooled. Our findings are presented below.

Patients and Methods

Over a period of about 18 months, HbA_{1c} assay was performed on blood samples collected for glucose as

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part of the OGTT from 401 non-pregnant patients (208 males, 193 females; age range 13 to 92 years) referred to the laboratories at North Manchester General Hospital (NMGH) and the Royal Liverpool and Broadgreen Hospitals (RLH). The majority of the requests for OGTT were from general practitioners (GPs) and, although they are advised to measure FPG before embarking on an OGTT, this is not always done. HbA_{1c} was measured using the Daiichi HA-8121 (NMGH) or HA-8140 (RLH) high performance ion-exchange chromatography (HPIEC) analysers (Biomen, Finchampstead, Berkshire, UK) with between-batch CV of less than 2 % at mean HbA_{1c} levels of 4.4 % and 8.2 %. The HA-8140 analyser is capable of identifying most of the more common haemoglobin variants and of eliminating them from the HbA_{1c} calculation. Assays on samples exchanged between the two laboratories showed very good agreement, differing on average by only 0.05 % (CV 2.2 %). The locally derived reference range for this method, applicable to both centres, was 3.8 to 5.5 %, which is in excellent agreement with ranges quoted by the manufacturer, derived from populations in Japan and Italy.

The OGTT was performed with patient preparation and result interpretation according to the recommendations of the World Health Organization (WHO)[6,7] with the exception that FPG was ignored and the emphasis placed on 2-h plasma glucose (2hPG) when classifying patients into one of the three categories: normal, impaired glucose tolerance (IGT, 8.9 to 12.1 mmol l^{-1} inclusive) or diabetes mellitus (DM,$\geqslant$12.2 mmol l^{-1}). The reason for this was to avoid misclassification due to inadequate fasting. Plasma glucose was measured on the Analox GM7 (Analox Instruments, London, UK) at NMGH and on the Beckman Glucose Analyzer (Beckman Instruments, High Wycombe, Buckinghamshire, UK) at RLH. Capillary blood was collected by finger-prick into a fluoride tube to preserve it and the same specimen was used for the assay of both glucose and HbA_{1c}.

Results

Of the 401 subjects tested, 178 had diabetic OGTT responses, 94 fell into the impaired glucose tolerance (IGT) category and 129 were normal. Based on these results, the prevalence of diabetes in the study group was about 44 % and IGT 23 %. A scatter plot of HbA_{1c} against 2h capillary plasma glucose (Figure 1) shows that only two patients with normal OGTT had HbA_{1c} above the upper reference limit of 5.5 % and that all 73 subjects with HbA_{1c} greater than 6.2 % had diabetic OGTT responses, although 105 of the people with OGTT diagnosed diabetes (59 %) had HbA_{1c} lower than this and 64 (36 %) had values within the non-diabetic range. All subjects in the IGT group had HbA_{1c} less than 6.3 % and 76 (85 %) had values within the non-diabetic range.

A plot of FPG against 2hPG for the same patients showed a similar relationship, but a few patients had high fasting levels not matched by diabetic 2 h levels

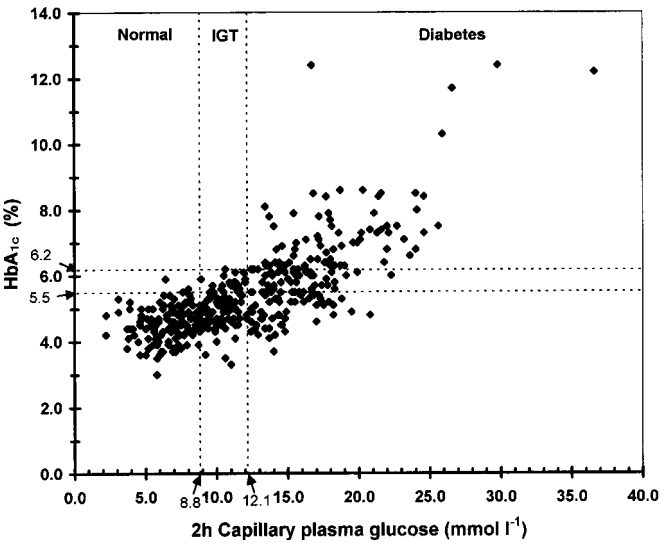

Figure 1. Plot of HbA_{1c} against 2 h capillary plasma glucose for 401 non-pregnant subjects undergoing OGTT. Horizontal broken lines represent diagnostic cut-off and upper limit of normal. Vertical broken lines indicate WHO diagnostic boundaries for IGT and diabetes

(Figure 2). In particular, one individual had FPG of 12.5 mmol l^{-1}, a 2 h capillary plasma glucose of 11.9 mmol l^{-1} and HbA_{1c} of 6.1 %.

Correlation coefficients between any two of the parameters (FPG, 2hPG and HbA_{1c}) were very similar (within the range 0.75 to 0.78) and highly significant ($p<0.001$). Statistics relating to diagnostic cut-off levels for HbA_{1c} and FPG are given in Tables 1 and 2 and receiver operating characteristic (ROC) curves in Figure 3. These show the effect on sensitivity and specificity of changing the cut-off levels and, although the area under the FPG curve is slightly greater than that under the HbA_{1c} curve, the curves cross and the sensitivity of HbA_{1c} becomes

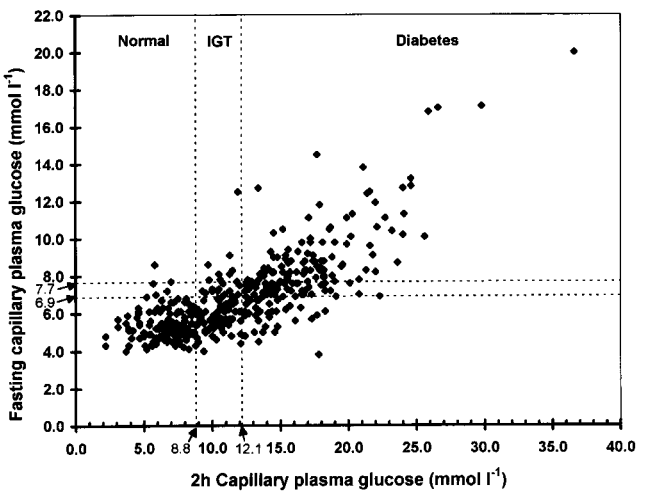

Figure 2. Plot of fasting capillary plasma glucose against 2 h glucose concentration in 401 non-pregnant subjects undergoing OGTT. Horizontal broken lines represent the older (higher) and newer (lower) diagnostic cut-off levels. Vertical broken lines indicate WHO diagnostic boundaries for IGT and diabetes

Table 1. Sensitivity and specificity figures for different cut-off values of HbA_{1c} as an indicator of diabetes in a non-pregnant population with a diabetes prevalence of 44.4 %

HbA_{1c} cut-off (%)	Sensitivity (%)	Specificity (%)
6.5	29.2 (23–36)	100.0
6.2	41.0 (34–48)	100.0
6.0	50.6 (44–58)	98.2 (97–100)
5.5	64.0 (57–71)	91.0 (87–95)
5.0	83.7 (78–89)	69.5 (64–76)
4.5	92.7 (89–97)	37.2 (31–44)
4.0	98.9 (97–100)	13.0 (9–17)
3.5	100.0	1.8 (0–4)

Figures in parentheses are 95 % confidence limits rounded to whole numbers.

Table 2. Sensitivity and specificity figures for different cut-off values of fasting capillary plasma glucose as an indicator of diabetes in a non-pregnant population with a diabetes prevalence of 44.4 %

FPG cut-off (mmol l^{-1})	Sensitivity (%)	Specificity (%)
12.5	5.6 (2–9)	100.0
11.0	10.7 (6–15)	99.6 (99–100)
10.0	15.7 (10–21)	99.6 (99–100)
9.0	23.6 (17–30)	99.1 (98–100)
8.5	31.5 (25–38)	98.2 (97–100)
8.0	44.4 (37–52)	96.9 (95–99)
7.7	51.7 (44–59)	96.0 (93–99)
7.5	61.8 (55–69)	94.2 (91–97)
7.0	73.6 (67–80)	89.2 (85–93)
6.9	78.1 (72–84)	87.9 (84–92)
6.5	83.7 (78–89)	80.3 (75–86)
6.0	89.9 (86–94)	65.9 (60–72)
5.5	95.5 (93–99)	51.1 (45–58)
5.0	96.6 (94–99)	29.1 (23–35)
4.5	98.9 (97–100)	11.2 (7–15)
4.0	99.4 (98–100)	0.9 (0–2)

Figures in parentheses are 95 % confidence limits rounded to whole numbers.

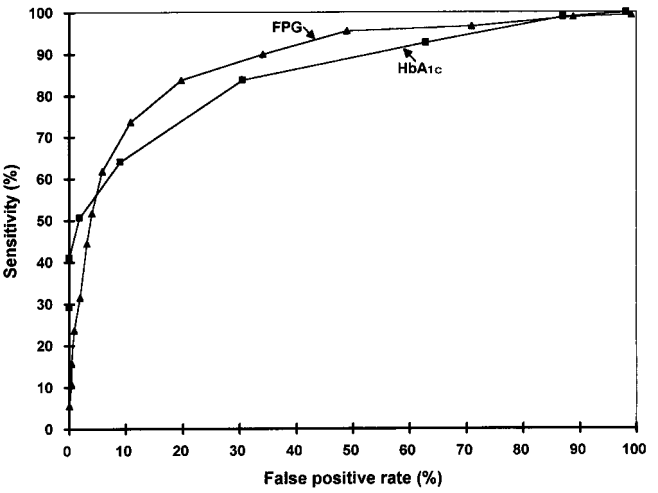

Figure 3. Receiver operating characteristic (ROC) curves for HbA_{1c} and fasting capillary plasma glucose as indicators of diabetes mellitus in non-pregnant subjects. The ROC curve shows the effect on sensitivity and specificity of changing the diagnostic cut-off levels

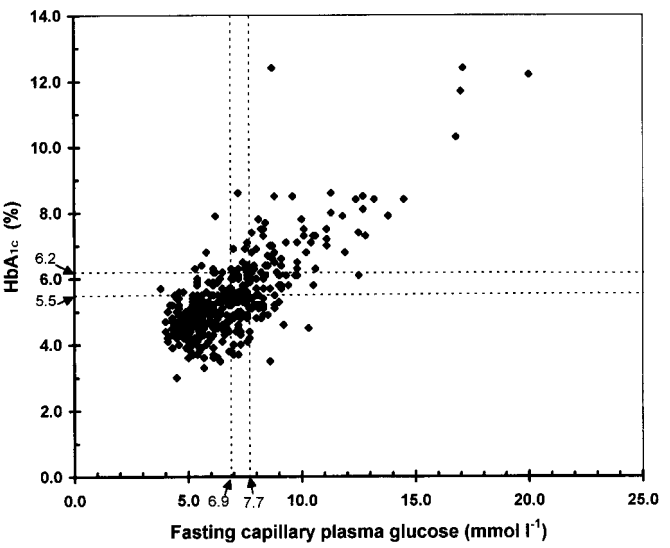

Figure 4. Plot of HbA_{1c} against fasting capillary plasma glucose for the study population. Horizontal broken lines represent diagnostic cut-off and upper limit of normal. Vertical broken lines represent the older (higher) and newer (lower) diagnostic cut-off levels

greater than that of FPG at high specificity (low false positive rate). A cut-off for HbA_{1c} at 6.2 % identified 73 of the 178 OGTT-diagnosed diabetic subjects, giving 100 % specificity, with a sensitivity for diabetes of 41 %. A cut-off at FPG of 7.7 mmol l^{-1} (equivalent to the WHO, 1985 FPG criterion of $\geq$7.8 mmol l^{-1}) had a sensitivity of 52 %, with specificity 97 %. The lower FPG cut-off at $\geq$7.0 mmol l^{-1}, proposed by some workers as an amendment to the WHO criteria and recently adopted by the American Diabetes Association,[1–3,5,8] classified 166 subjects as diabetic, but 27 of these were not positive by OGTT, giving a sensitivity of 78 % and specificity of 88 %.

The plot of HbA_{1c} against FPG (Figure 4) shows that some patients (100) had high FPG (>6.9 mmol l^{-1}) with HbA_{1c} <6.3 %, but in about a quarter of these (26) the 2hPG was not indicative of diabetes, i.e. the HbA_{1c} was in keeping with the 2hPG glucose, but the FPG was not. Twenty-two of these subjects had IGT, but 4 had normal 2hPG. Conversely, there are 18 coordinates with HbA_{1c}>6.2 %, but FPG <7.8 mmol l^{-1} (7 with HbA_{1c}>6.2 % and FPG<7.0 mmol l^{-1}). All these patients had diabetic 2hPG figures.

The lower right section of Figure 4 shows three points with low HbA_{1c} and high FPG that are separate from the main body of observations. In one case, FPG (8.6 mmol l^{-1}) is out of line with the other two parameters (HbA_{1c} 3.5 %, 2hPG 5.8 mmol l^{-1}), but in the others 2hPG supports the FPG figures, indicating diabetes and raising the possibility that the HbA_{1c} in these two

might be artificially low because of the presence of a haemoglobin variant.

Table 3 shows the distribution of the 401 subjects in the diagnostic categories according to 2hPG figures and separately according to the ADA FPG criteria. From the implied prevalence figures, there is apparently better agreement between the two methods for diagnosing diabetes than there is for diagnosing IGT/IFG or normal categories. Looking at the figures in more detail, however, we found that the diabetes prevalence according to FPG was influenced by 27 out of the 166 positives being false, as judged by 2hPG, and this was counterbalanced by 39 false negatives, the difference accounting for the overall slightly lower prevalence figure produced by FPG. Only 139 subjects were positive by both criteria, whereas 178 were positive by the 2hPG in the OGTT (i.e. FPG sensitivity 78 %).

Although 94 of our subjects were classified as IGT by the 2hPG and 70 subjects had IFG (FPG in the range 6.1 to 6.9 mmol l^{-1}), only 27 individuals were positive by both of these criteria. Figure 2 clearly shows that those who would be classified as IFG span quite a wide spectrum from normal, through IGT to diabetic, when assessed by 2hPG in the OGTT.

One patient, subsequently excluded from the study because of inconsistent findings, had an initial OGTT response indicative of IGT (2 h capillary plasma glucose 11.3 mmol l^{-1}), but an HbA_{1c} of 7.3 %. She suffered from asthma, had received prednisolone therapy and had had a toe amputated because of vascular problems. A repeat OGTT 3 months later gave a diabetic response (2hPG 14.5 mmol l^{-1}) and the HbA_{1c} was then 7.2 %, virtually identical to the earlier result. FPG concentrations were 4.5 and 3.9 mmol l^{-1} on the two occasions.

Discussion

Hitherto, most attempts to use HbA_{1c} diagnostically have been either in the context of population screening for case-finding or as a straight diagnostic substitute for the OGTT. In the former situation, one may wish to pick up as many true positives as possible, at the risk of including some false positives who could be eliminated later by more rigorous testing using the OGTT. In this case, a highly sensitive test is needed, but specificity is not quite so important. On the other hand, as a straight substitute for the OGTT, HbA_{1c} would have to be both sensitive and specific.

Table 3. Classification of the 401 patients according to OGTT 2hPG and ADA FPG criteria to show the degrees of concordance and discrepancy between the two methods

		Classified by OGTT 2hPG				
		Diabetes	IGT	Normal	Total	Implied prevalence
Classified by ADA FPG	Diabetes	139	22	5	166	41.4 %
	IFG	21	27	22	70	17.5 %
	Normal	18	45	102	165	41.1 %
	Total	178	94	129		
	Implied prevalence	44.4 %	23.4 %	32.2 %		

Our results show that HbA_{1c} does not fully meet the criteria for either of these applications, but, at a lower degree of sensitivity, it does become very specific, allowing it to be used to say, with considerable confidence, that an individual whose HbA_{1c} is above a certain value (6.2 % by the method employed in this study) is diabetic. This would not, however, imply that subjects with lower values are normal, because they may still have diabetes or IGT, as judged by their response in the OGTT. Indeed, approximately one-third of our patients classified as diabetic by the OGTT had HbA_{1c} figures below 5.5 % and this highlights a diagnostic paradox.

Patients diagnosed as diabetic by OGTT, but with HbA_{1c} within the normal range, would not be given insulin or drug therapy, although they may be given dietary advice. Are these people diabetic or not? By our current definition, they are, but this is based on challenging a person with the ingestion of a non-physiological load of glucose (although it may be matched by some commonly available proprietary high-energy drinks), so it is not surprising that they may have inadequate tolerance of such a load while still being able to deal satisfactorily with more conventional dietary carbohydrate. Whether they should be classified as diabetic in the absence of evidence of sustained hyperglycaemia may be argued. Most authorities would agree that the basis for classification of individuals as diabetic should be their risk of developing microvascular, and perhaps macrovascular, complications and there is evidence from the Diabetes Control and Complications Trial (DCCT) that lower HbA_{1c} levels are associated with reduced risk of retinopathy in IDDM.[9] A recent survey of Pima Indians showed that 2 h plasma glucose, fasting plasma glucose, and glycated haemoglobin had similar abilities for predicting the development of retinopathy and nephropathy. The authors concluded, therefore, that FPG and glycated haemoglobin were as useful diagnostic tools as the OGTT.[10] There are, however, considerable differences between the levels of diagnostic sensitivity and specificity reported for glycated haemoglobin in the literature. In our study, and in others,[11–13] HbA_{1c} was not as sensitive at high specificity as has been claimed elsewhere.[14] These differences may, in part, be attributable to glycated haemoglobin method differences, but most of the available evidence suggests that glycated haemoglobin is slightly less sensitive than FPG for diagnostic purposes.

A large-scale meta-analysis, using data from 10 different studies employing different HbA_{1c} methods, concluded that a HbA_{1c} cut-off at 7.0 %, using a method with a reference range of 4.3 to 6.3 %, was a reasonable approach to identifying diabetes requiring pharmacological rather than merely dietary treatment and could be

used instead of the OGTT.[14] Allowing for reference range differences, our figure of 6.2 % is roughly equivalent to this cut-off.

It is well-recognized that the OGTT is an imperfect test, especially as a reference method, being influenced by a number of factors that are difficult to control and subject to significant intraindividual variation from one occasion to another.[15,16] One of our cases illustrates this point and would support the argument in favour of HbA_{1c} as a diagnostic test.

In keeping with previously published data,[1–3] we found FPG to be quite sensitive as an indicator of diabetes and, if a specificity of around 88 % is acceptable, then the diagnostic cut-off of $\geq$7.0 mmol l^{-1} proposed by the ADA will achieve this at a sensitivity of up to 78 %. False positives, presumed to result from inadequate fasting, limit its diagnostic potential. If patient compliance could be assured, FPG would be a more reliable diagnostic test, but our finding that both HbA_{1c} and 2hPG could sometimes be abnormally increased without apparent elevation of FPG suggested that HbA_{1c} in these cases was a better diagnostic guide.

Ultimately, the choice of diagnostic test for diabetes mellitus will depend on the circumstances under which it is being performed, on confidence in patient compliance and on availability and affordability of the different methods. FPG is much cheaper than HbA_{1c}, but only limited confidence can be placed in a single positive result and the ADA specifies that repeat testing is necessary.[4] On the other hand, we have demonstrated that it is possible to choose a cut-off for HbA_{1c} (6.2 % for our method), above which we can be very confident that an individual has diabetes. In this way, over 40 % of diabetes in our non-pregnant population could be identified with no false positives. This figure could be raised to over 50 % using a HbA_{1c} cut-off of 6.0 %, if 2 % false positives (all IGT classified as diabetes) were considered acceptable. If the upper limit of normal (5.5 %) were employed as a cut-off, 64 % sensitivity could be expected with still only 9 % false positives, most of which would be IGT. Hence, any cut-off above the upper limit of normal would underestimate the prevalence of diabetes in the population, so HbA_{1c} cannot be used in epidemiological studies. Indeed, some subjects with abnormal OGTT have non-diabetic HbA_{1c} values (36 % of those with diabetes and 81 % of those with IGT) and the test cannot, therefore, be used to exclude diabetes as currently defined. However, there is evidence that this also applies to FPG unless the value is below about 4.4 mmol l^{-1}.[2] Figure 2 clearly shows a considerable number of subjects with FPG less than the ADA 'cut off' of 6.1 mmol l^{-1}, but who nevertheless had diabetic 2hPG levels.

Some of the patients in our study could have been diagnosed by random or fasting plasma glucose alone but even FPG produced some false positives. Most laboratories find themselves carrying out a proportion of unnecessary OGTTs, and this could be reduced by HbA_{1c} screening. The cost of the assay itself may be offset by the reduction in administration costs! Patients identified as having diabetes by HbA_{1c}, and eliminated from further testing, would reduce the number of non-pregnant subjects requiring OGTT or other fasting measurements by approximately one-fifth.

The main disadvantages of using HbA_{1c} diagnostically are difficulties of standardization, and the possibility of samples containing haemoglobin variants that might give spurious results. There is also the theoretical possibility that a new case of diabetes might not have had time to develop a significantly raised HbA_{1c}. Some of these problems should be overcome by current efforts at increased international co-operation on standardization and improvements in method specificity. If these aims can be achieved, the diagnostic emphasis in future ADA and WHO reports could shift from FPG towards HbA_{1c}.

The FPG cut-off at 7.0 mmol l^{-1}, recommended by the ADA, would give a prevalence for diabetes of 41.4 % in our population, compared with 44.4 % by OGTT (Table 3). The ADA also found that the FPG would diagnose fewer cases of diabetes than the OGTT. Although the prevalence figures with the two tests are very similar, they do not always identify the same people. Compared with the 2hPG results, the ADA FPG criteria produced 27 false positives and 39 false negatives that, to some extent, balanced each other out and became hidden in the prevalence figure. While the ADA acknowledges this, it provides no evidence as to the extent of the problem and no reference.[4] Furthermore, the category of 'impaired fasting glucose' (IFG) that has been introduced does not, in our data, correspond to IGT. If the OGTT is abandoned for routine diagnostic purposes, the category of IGT will probably disappear. This is important because IGT has been implicated as a risk factor for macrovascular disease. When better comparability between different HbA_{1c} methods has been achieved, a large-scale multicentre study to re-examine the risks associated with different levels of glycaemia might prove informative.

In summary, we believe we have demonstrated that a precise, reliable HbA_{1c} method can be used as a first-line diagnostic test for diabetes and is superior to FPG in terms of its specificity above a certain cut-off value. It requires no patient preparation. It is, however, less sensitive than FPG and would be better as a test to reduce the number of OGTTs required, rather than as a direct substitute for the OGTT, because normal HbA_{1c} values do not exclude diabetes as defined by the WHO OGTT criteria.[6] At present there is insufficient information in the literature to assess accurately the risk of developing complications at different levels of HbA_{1c}, but if this becomes available, we may come to rely on HbA_{1c} for diagnosing diabetes requiring treatment or, more correctly, 'risk-associated glycaemia' (RAG). This would revise our definition of what we consider to be diabetes, affecting established population prevalence figures. We are at a crossroads in the diagnosis of diabetes and

whatever path we take, we are likely to be selecting a slightly different population to label as diabetic from that identified by current WHO criteria.

Acknowledgement

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